The Reflex Sympathetic Dystrophy Syndrome Association estimates that the CRPS affects between 200,000 and 1.2 million Americans. The underlying causes of the syndrome have yet to be defined, and no definitive diagnostic test exists even though CRPS was first described in the late 19th century by the neurologist Silas Weir Mitchell. Mitchell referred to the cluster of symptoms he noticed in some of the Civil War soldiers who were under his care as "causalgia."  

"We're lost in the woods here about the causes of complex regional pain syndrome [CRPS], because the definitive trials could cost millions and the NIH is not funding pain research now," said R. Norman Harden, MD, director of the Center for Pain Studies, Rehabilitation Institute of Chicago. What to do? The Reflex Sympathetic Dystrophy Syndrome Association estimates that the CRPS affects between 200,000 and 1.2 million Americans. The underlying causes of the syndrome have yet to be defined, and no definitive diagnostic test exists even though CRPS was first described in the late 19th century by the neurologist Silas Weir Mitchell. Mitchell referred to the cluster of symptoms he noticed in some of the Civil War soldiers who were under his care as "causalgia."  

The soldiers persistently complained of severe, burning pain long after their wounds had healed. They also experienced swelling, redness, and temperature fluctuations at the injured site, typically a limb. More than a century later, in 1994, the International Association for the Study of Pain (IASP) gave the syndrome its official name-complex regional pain syndrome-and developed clinical criteria for diagnosis. Confusion about CRPS remains, however, and may be part of a larger shortcoming related to overall pain management. "Physicians know very little about pain in general and even less about CRPS," said Anne Louise Oaklander, MD, PhD, associate professor of neurology at Harvard Medical School in Boston.  

**DIAGNOSTIC CRITERIA**

CRPS has 4 diagnostic criteria. The first-which is not necessary for diagnosis-is the presence of trauma or a cause of immobilization. Second is continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event. Third is evidence of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain. Fourth is the exclusion of other conditions that would account for the degree of pain and dysfunction.  

The IASP further divides CRPS into CRPS I, in which major nerve damage is not present, and CRPS II, in which major nerve damage is present. CRPS II replaces Mitchell's old term "causalgia," while CRPS I replaces the term "reflex sympathetic dystrophy," which was introduced in 1946 by a Boston physician named James Evans. At least one neurologist rejects the IASP criteria, specifically for the diagnosis of CRPS I. "You diagnose CRPS I only when there is no medical explanation for the symptoms," said Jose Ochoa, MD, PhD, professor of neurosurgery and neurology at the Oregon Health and Science University and director of the Neuromuscular Unit at Legacy Good Samaritan Hospital and Medical Center in Portland, Oregon. He said that such a diagnosis of exclusion is illogical. In his view, it means that the clinician simply has failed to diagnose the true cause of pain-whether it be nerve injury, arthritis, phlebitis, hysteria, or malingering. But most physicians accept the criteria, although it is possible that the definitions could change as clinicians gain a better understanding of the syndrome. "In time, we may recognize half a dozen different kinds of CRPS, not just two," said Ricardo A. Cruciani, MD, PhD, vice chair of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York City.  

**A CLINICAL DIAGNOSIS**

Diagnosis of CRPS is clinical, based on the patient's history and examination findings. "This is a disease that really puts a premium on the clinical diagnostic skills of the neurologist because there is no MRI scan or electromyography study that can make this diagnosis," said Oaklander. Neurologists should look for focal signs of nerve injury, such as weakness, loss of pin sensation, reflex changes, or Tinel signs, explained Oaklander. They can check for mechanical allodynia with a
light touch and for temperature allodynia using test tubes of warm and cool water. The clinician should also take note of trophic changes to the skin, nails, and hair and look for signs of autonomic disturbance, such as neurogenic edema or the differences in temperature or color in the patient's limbs.

Thermography or a spot temperature measurement can be used to document vasomotor autonomic disturbances. Changes in perspiration can be assessed by dragging a smooth-handled instrument across the skin of the affected and unaffected side; the instrument will glide more easily over sweaty skin than dry skin. The clinician may also note decreased range of motion, weakness, dystonia, tremor and, in some cases, myoclonic activity.

Bone scans and sympathetic nerve blocks do not aid in diagnosis, but some clinicians will use a 3-phase bone scan to reveal whether CRPS has resulted in osteopenia and use a sympathetic nerve block to determine whether the sympathetic nervous system is involved—which it is in about 20% of cases, according to Cruciani. In addition, Oaklander said that she will occasionally do a somatic nerve block to identify exactly which nerves have been damaged. Radiographs should be used only in cases where an orthopedic problem is suspected to be the cause of the syndrome.

**POSSIBLE CAUSES**

CRPS is usually triggered by an injury such as a fracture, sprain, crush injury, or penetrating injury. Oaklander pointed out that even something as innocuous as having blood drawn can lead to CRPS, as can undergoing a surgical procedure. "Damage to cutaneous sensory nerves has been shown to be the culprit, but we don't understand why only very rare patients are left with problems after such routine procedures," she said.

What exactly goes wrong in CRPS is poorly understood. It has alternatively been explained as a hypersensitization of the CNS, an inflammatory process, and a disorder of the sympathetic nervous system. According to Cruciani, constant pain signals from the periphery may lead to changes in the posterior horn of the spinal cord, such as an increase in the number of N-methyl-d-aspartic acid (NMDA) receptors that bind glutamate, an increase in the number of certain types of sodium channels, or a change in the expression of the calcitonin gene-related peptide. An increase in proinflammatory cytokines also has been identified. "All of these changes at the molecular level may have a correlate in the excitability of the somatosensory cortex," he said, explaining that plastic changes in this area have been correlated with chronic pain.

One hypothesis is that the pain of CRPS I is caused by undetected nerve injuries. In an effort to identify these injuries, Oaklander undertook a skin biopsy study of 18 adults with CRPS I and 7 osteoarthritic patients with disabling leg pain, swelling, and disuse. "We found anatomical evidence that patients with CRPS I had fewer sensory nerve endings in the epidermis of their painful CRPS-affected area than in nearby control areas," reported Oaklander.

It is not clear, however, whether these nerve changes are the cause of CRPS I or a consequence. Harden, who also is associate professor in the Department of Physical Medicine and Rehabilitation at Northwestern University Feinberg School of Medicine, Chicago, argued that the changes are probably a consequence: "The most likely explanation is that these people have this intense vasoconstriction from the disease . . . and this causes a dying back of the nerves," he said. Oaklander agreed that cause and effect remain unclear but pointed out that her study found no evidence of nerve losses in the control group with other painful injuries.

**SOMATIZATION?**

One of the biggest controversies in CRPS is the role of the mind. Some experts maintain that CRPS often has a psychogenic cause, such as depression, "Fifty percent of people with chronic pain are depressed," said Cruciani. It's unclear, however, whether depression is a cause or a consequence of the syndrome. Sociologic considerations also may play a role, especially if the patient has a financial incentive to be disabled.

"I would say that it is a biomedical disease, a psychological disease, and a sociologic disease," said Harden. "It is all of those things in every patient; it's just to be determined in what measure."

By contrast, Robert J. Schwartzman, MD, chair of Neurology at Drexel University College of Medicine in Philadelphia, remarked that "it's never, ever psychiatric. When you have severe pain that totally wrecks your life, you're depressed."

Oaklander took a slightly different approach, pointing out that if the patient's chronic pain can be attributed to a psychogenic cause, the condition is not CRPS. She also cautioned neurologists not to attempt to make psychiatric diagnoses. She pointed out that the country's current disability system discourages patients from recovering. She echoed the idea that there might be economic reasons why patients maintain their disability. However, she said that she did not encounter malingering any more frequently among patients with CRPS than among patients with any other medical condition.
TREATMENT STRATEGIES

Treatment of CRPS usually involves several specialists, all of whom must have expertise in the syndrome. For example, Cruciani, who works at a referral center for patients with CRPS, reports that his team includes neurologists, anesthesiologists, rehabilitation experts, psychiatrists, and a psychologist. "You have to have a team that's knowledgeable about CRPS and how to treat it," said Harden. "If you don't have that kind of team in place, you fail."

Treatment of CRPS is far from straightforward. The FDA has not approved any pharmacologic or interventional treatments. The most common therapies, however, are medication, physical rehabilitation, and nerve blocks. Some patients also undergo spinal cord stimulation, drug pump implantation, or other surgery.

Medication. Many of the drugs used in CRPS are chosen based on their success in treating other types of neuropathic pain disorders, such as diabetic retinopathy and postherpetic neuralgia. For example, opioids, the anticonvulsant gabapentin (Neurontin), and tricyclic antidepressants have not been evaluated for treatment of CRPS but are often used because randomized clinical trials have shown them to be effective in treating other neuropathic conditions.

Although opioids are the gold standard for treating acute pain, their use is highly controversial in CRPS. "We know that opioids cause hyperalgesia," said Harden. "If you have a drug that causes hyperalgesia and a disease that is characterized by hyperalgesia, how logical is it to use that drug in that disease?" Oaklander agreed that it was theoretically possible for opioids to worsen CRPS, but she said that this should not prevent physicians from prescribing opioids for certain patients who have CRPS. She did, however, caution that the lowest effective dose should be used. Some pain specialists advocate the use of methadone for the management of CRPS, according to Cruciani. Another possibility is an opioid in combination with an NMDA antagonist such as memantine (Namenda).

The best-studied treatment for early CRPS is the bisphosphonate drugs. Placebo-controlled studies have shown improvements in active movement and motor function with intranasal calcitonin, intravenous clodronate, and intravenous alendronate (Fosamax); one placebo-controlled study showed no improvement with intranasal calcitonin. Clodronate may be the most effective because it acts on several inflammatory mediators. However, Oaklander pointed out that bisphosphonates have not been tested for use in chronic CRPS.

Another common treatment for CRPS is systemic corticosteroids. In a study of 23 patients, 30 mg/d of oral prednisone was significantly more effective than placebo was. "We use that strategy to break the cycle of pain when a patient goes into a flare," said Cruciani.

Several studies have looked at topical medications for CRPS. One study found topical dimethyl sulfoxide to be as effective as an oral free radical scavenger. Topical lidocaine patch also was effective in an open-label study. Experimental medications for CRPS include thalidomide, which has not yet been studied in controlled trials; etanercept (Enbrel); ketanserin; and ketamine. In a highly controversial procedure, Schwartzman sent 31 patients to Germany to be treated with anesthetic doses of ketamine that produce a coma lasting 5 days. Schwartzman reported that 10 of those patients are now cured, including 1 who has been in remission for 9 years. Adverse effects included hallucinations and flashbacks; potential complications include memory loss, pneumonia, blood clots, and stroke. Harden said that most clinicians view the ketamine coma treatment as questionable, but that its true value would remain unknown until randomized controlled trials are performed.

Schwartzman also has developed a 10-day course of intravenous ketamine that is delivered on an outpatient basis. Positive results were achieved in an open-label study. He said that he and his team have used the treatment in about 150 outpatients.

Cruciani pointed out that ketamine has been helpful in the treatment of postherpetic neuralgia. He cautioned that the drug has significant adverse effects and that most patients would be unable to tolerate it in doses high enough to control the pain of CRPS.

Physical rehabilitation. Most experts stress the importance of physical rehabilitation, including both physical and occupational therapy. Rehabilitation should be started immediately or as soon as medication has had a chance to relieve the most severe pain.

"The most important thing is physical therapy," said Cruciani. "Not only do physical therapy and exercise improve CRPS in the affected limb, they also prevent it from migrating to other parts of the body." Cruciani refers patients with CRPS of the lower extremities to physical therapists and patients with CRPS of the upper extremities to occupational therapists. The goals of physical rehabilitation include minimizing edema, normalizing sensation, promoting normal positioning, and decreasing muscle guarding.

Nerve blocks. Nerve blocks for CRPS usually contain local anesthetics—either alone or in combination
with clonidine, NSAIDs, corticosteroids, bretylium, or guanethidine. There are no universally accepted guidelines for the use of lumbar sympathetic or stellate ganglion nerve blocks, and the quality of published reports is generally poor. However, some clinicians do use nerve blocks in select cases, especially if pain is severe enough despite treatment with oral medication to interfere with physical or occupational therapy. If a nerve block is effective in decreasing pain, the clinician may want to consider repeating the treatment. However, there is no convincing evidence to support the use of long-term treatment with nerve blocks.

"Sympathetic nerve blocks can relax the blood vessels and give temporary relief, but meta-analysis shows that there's no evidence of long-term disease modifying benefits," said Oaklander, who advised that patients receive only a few.

**Spinal cord stimulation.** Many experts recommend the use of spinal cord stimulators in CRPS, especially for patients who are responsive to sympathetic blocks. Research on the stimulators is far from conclusive, however. In the one randomized trial conducted on spinal cord stimulation for CRPS, patients assigned to spinal cord stimulation plus physical therapy had a significant reduction in pain compared with those assigned to physical therapy alone. Harden argues that 1 trial is not enough to go on for clinical decision making. "The study suggests that perhaps spinal cord stimulation works a little bit better than physical therapy alone, but it's unclear what the nature of the control treatment was." He said that given the risks and high cost of implanting a surgical device, more studies are needed. "You should not be charging $40,000 for an implanted device like this without more evidence," he said.

Still, many experts find the devices to be beneficial. "We use a lot of spinal cord stimulation," said Cruciani. He said that the treatment works well in the limbs but is less effective for pain in the center of the body. In addition, Oaklander said that she often recommends the stimulators but cautioned that they are expensive, invasive devices that do not help all patients. She conceded that more research is needed to determine how the devices work and which patients are most likely to benefit.

**Implanted drug pumps.** Implanted drug pumps are even less well studied than spinal cord stimulators, with most research consisting of case reports. The implanted pumps that deliver opioids can be useful for someone with pain that responds best to treatment with an opioid but who develops intolerable adverse effects from taking it as a pill," said Oaklander. "We also consider baclofen pumps for patients with intractable CRPS dystonia that's too widespread to be treated with botulinum toxin [Botox]... so there is a very specific and limited number of patients for whom that might be an appropriate treatment." Cruciani, by contrast, said that he has many patients on the pumps in his group practice. He pointed out that in addition to opiates, clonidine, baclofen, and bupivacaine independently or in combination could be administered by pumps. He also has treated several patients with ziconotide (Prialt), a new drug that has been advocated for patients whose pain is resistant to opioid therapy or who develop intolerable adverse effects from opioids.

**Surgery.** A number of surgical approaches have been attempted in an effort to cure CRPS. "The most effective treatment for painful nerve injury is surgery, when indicated," said Ochoa, such as in the case of surgery to decompress a trapped median nerve, manage a neuroma, or manage a tumor or disk compressing a nerve.

Cruciani agreed that surgery is essential when a clear surgical cause can be found. However, he estimated that only about 10% of CRPS cases can be addressed surgically. "It tends to be the exception more than the rule," he said. Some surgeons have performed sympathectomy in an effort to resolve pain, but results of published reports are not encouraging. In some cases, the procedure may lead to a worsening of pain.

**PROGNOSIS**

Most experts agree that with treatment, most patients can expect their CRPS to improve. "There's a misconception that personal injury lawyers would like to promulgate, which is that CRPS is lifelong and completely disabling," said Harden. With proper treatment, patients could get on with their lives, he said. Because patients go into remission as opposed to being cured, patients need to stay active, engage in physical and occupational therapy, and possibly take medication and continue with other treatments that have helped, he added.

Cruciani estimated that with treatment, about 20% of patients go into remission. "Then you have about 40% to 50% of patients who are stabilized. Although they continue to have pain and are uncomfortable, they can function to a certain degree. Then you have 30% for whom it doesn't matter what you do; they're miserable."

Oaklander pointed out that she never sees geriatric patients with CRPS; the average age of most patients is about 40, and the prevalence decreases as patients age. "These kind of epidemiologic data are consistent with a disease that does not last forever," she said. "It's one of the things that
keeps me optimistic."

REFERENCES


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